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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SANOFI-AVENTIS DEUTSCHLAND GMBH, AVENTIS PHARMA S.A., ABBOTT GMBH & CO. KG, and ABBOTT LABORATORIES, Plaintiffs, v. GLENMARK PHARMACEUTICALS INC., USA, and GLENMARK PHARMACEUTICALS LTD. Defendants.	Civil Action No. 07-CV-05855 (DMC-MF)

PLAINTIFFS' MEMORANDUM OF LAW IN OPPOSITION TO GLENMARK'S MOTION FOR SUMMARY JUDGMENT THAT CLAIMS 1-4, 7 AND 10 OF U.S. PATENT 5,721,244 ARE INVALID

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

CASES

Page(s)

STATUTES

PRELIMINARY STATEMENT

Plaintiffs submit this brief in opposition to defendants Glenmark Pharmaceuticals Inc., USA and Glenmark Pharmaceuticals Ltd.'s ("Glenmark") motion for summary judgment that claims 1-4, 7 and 10 of the U.S. Patent No. 5,721,244 ("the '244 patent") are invalid.

The '244 patent discloses and claims pharmaceutical compositions containing an angiotensin-converting enzyme inhibitor ("ACE inhibitor") having certain bicyclic or tricyclic ring systems and a calcium antagonist (also known as a calcium channel blocker or "CCB") in amounts effective to treat hypertension. (Pls.' Stmt.[1] ¶ 2) One claimed embodiment is a composition of quinapril, an ACE inhibitor, and a calcium antagonist. (*Id.* ¶ 4.) Another embodiment is a composition of trandolapril, another ACE inhibitor, with a calcium antagonist. (*Id.*)

This patent infringement case arises from Glenmark's attempt to make a copycat drug product of Tarka®, which is protected by the '244 patent. Tarka® contains trandolapril and verapamil hydrochloride, a calcium antagonist. (Pls.' Stmt. ¶ 10.) Glenmark has already stipulated to infringement of claims 1-4, 7 and 10 of the '244 patent -- the asserted claims in this case. Glenmark now makes a motion asking the Court to grant summary judgment that these claims are invalid on the ground of obviousness. Its motion is utterly baseless. Glenmark seeks to avoid trial on material fact issues underlying the obviousness inquiry, including the level of ordinary skill in the art, the scope and content of the prior art, the differences between the prior art and the patented invention, and secondary considerations such as unexpected results and commercial success. Each of these fact elements is disputed.

[1] "Pls.' Stmt." refers to Plaintiffs' Statement of Material Facts in Support of Their Opposition to Glenmark's Motion for Summary Judgment submitted herewith.

Glenmark's expert, Dr. Clive Rosendorff, who is a physician, opines that a person of ordinary skill in the art pertaining to the '244 patent excludes a chemist (Rosendorff Decl.[2] ¶ 27) even though the '244 patent discloses and claims complex chemical formulas, and even though he admits that without knowledge of chemistry one would not even understand the scope of the claims of the '244 patent. (Pls.' Stmt. ¶ 18.) Plaintiffs' experts, Dr. Robert Piepho (a pharmacologist), Dr. Robert Carey (a physician), and Dr. Jeffrey Winkler (a chemist), all disagree with Dr. Rosendorff's opinion. (*Id.* ¶ 14.)

Glenmark concedes that the prior art fails to disclose the patented pharmaceutical composition containing quinapril and a calcium antagonist or any other composition within the scope of the claims of the '244 patent. Yet, it argues that it would have been obvious for one skilled in the art to choose a particular compound within this claim scope, quinapril, from all of the hundreds of available ACE inhibitor compounds known at the time, and substitute it for captopril, enalapril or lisinopril (all ACE inhibitors) in the prior art disclosing these compounds in combination with a calcium antagonist. Glenmark, however, ignores the significant differences in chemical structure between quinapril and these compounds. (*See* Rosendorff Decl. ¶ 45.) These structural differences affect the physical and biological properties of the molecules, and as a result, one of ordinary skill would not be able to predict reasonably how these differences could affect the activity of the ACE inhibiting compounds in combination with a calcium antagonist. (Pls.' Stmt. ¶¶ 21-38.)

Indeed, Glenmark completely glosses over the fact that the U.S. Patent and Trademark Office ("PTO") considered what Glenmark acknowledges to be the closest prior art -- namely the enalapril and calcium antagonist combination disclosed in the Garthoff reference --

[2] "Rosendorff Decl." refers to the Declaration of Clive Rosendorff dated July 24, 2009.

and granted the '244 patent because of significant structural differences between the compounds of the '244 patent and enalapril. (Pls.' Stmt. ¶¶ 41-42.) Glenmark's only retort is Dr. Rosendorff's bare assertion that one skilled in the art would not have been concerned with structural differences. (Rosendorff Decl. ¶ 45.) But the PTO rejected this position and each of plaintiffs' experts vigorously disagrees with Dr. Rosendorff. (Pls.' Stmt. ¶¶ 33, 41-42.)

Glenmark also misconstrues the scope and content of the prior art. As explained by plaintiffs' experts, the prior art references relied upon by Glenmark, as understood by a person of ordinary skill in the art, fail to disclose or suggest a "pharmaceutical composition" containing quinapril and a calcium antagonist "in amounts effective to treat hypertension," as required by the claims of the '244 patent. (Pls.' Stmt. ¶¶ 47-84.) Hypertension is a life-long disease. Hence, to treat it, the drug substance must be effective in reducing chronic high blood pressure and maintaining its efficacy long term. (*Id.* ¶ 7.) Short term or acute blood pressure lowering studies would not establish the long-term efficacy of the tested substances. (*See id.* ¶ 76.) The prior art references relied on by Glenmark, however, described acute studies and did not demonstrate that the combinations were effective to treat hypertension. (*Id.*) Dr. Rosendorff even conceded that the data presented in the prior art would not have led one skilled in the art to use the prior art enalapril and calcium antagonist combinations to treat hypertension with a reasonable expectation that such treatment would be successful. (*Id.* ¶ 69.)

Glenmark also fails to acknowledge that at the time of the invention, October 1986, the state of the art did not recommend using a "pharmaceutical composition" of an ACE inhibitor and a calcium antagonist -- *i.e.*, a combination of these two substances in a single dosage form, such as a tablet -- to treat hypertension. (Pls.' Stmt. ¶ 112.) Instead, the recommended and accepted treatment was the so-called stepped care approach. (*Id.*) Under this

approach, a single antihypertensive agent, *i.e.*, a thiazide diuretic or beta-blocker, was used as initial therapy, and if this treatment failed, one or more subsequent agents were administered to the patient. (*Id.* ¶ 115-17.)

But even with the stepped care approach, at the time of the invention, the only recommended ACE inhibitors were captopril and enalapril, and they were used only in limited cases and only when initial therapy failed. (*See* Pls.' Stmt. ¶ 118.) In addition, calcium antagonists were not included in the stepped care approach. (*Id.*) And quinapril and trandolapril were not recommended until 1993 and 1997, respectively. (*Id.* ¶ 119.) In fact, as Dr. Carey explained, a pharmaceutical composition (*i.e.*, in a single dosage form) of an ACE inhibitor and a calcium antagonist was not recommended for treating hypertension until 1997 -- ten years after the invention of the '244 patent. (*Id.* ¶ 120.)

Glenmark also ignores the fact that ACE inhibitors are not alike (*id.* ¶¶ 89-103), and at the time of the '244 patent invention, there was a myriad of unpredictable options available, and one skilled in the art would not have chosen quinapril from amongst the hundreds of published ACE inhibitors for combining with a calcium antagonist. (*See id.* ¶¶ 85-88.)

Finally, the claimed invention exhibits unexpected and advantageous properties, including surprisingly longer duration of action than the prior art enalapril and calcium antagonist combinations. (*See* Pls.' Stmt. ¶¶ 128-32.) Tarka® -- a drug product within the scope of the asserted claims -- is also a commercial success, whereas the prior art enalapril and calcium antagonist combinations have been dismal commercial failures. (*Id.* ¶¶ 157-59.) And no captopril or lisinopril combination with a calcium antagonist has ever been marketed. (*Id.* ¶ 159.)

"Summary judgment is granted only if all probative materials of record, viewed with all inferences in favor of the non-moving party, demonstrate that no genuine issues of material fact exist and that the movant is entitled to judgment as a matter of law." *Novartis Pharm. Corp. v. Teva Pharm. USA, Inc.*, 2009 WL 483865, at *2 (D.N.J. Feb. 25, 2009) (Cavanaugh, J.); *see also Celotex Corp. v. Catrett*, 477 U.S. 317, 330 (1986); Fed. R. Civ. P. 56(c). Applying this standard, plaintiffs respectfully submit that Glenmark's summary judgment motion should be denied.

STATEMENT OF FACTS

For their statement of facts relevant to the disposition of this motion, plaintiffs respectfully refer the Court to the accompanying Plaintiffs' Supplemental Statement of Disputed Facts in Support of Their Opposition to Glenmark's Motion for Summary Judgment that Claims 1-4, 7 and 10 of U.S. Patent 5,721,244 Are Invalid dated September 21, 2009.

ARGUMENT

I. Glenmark Is Not Entitled to Summary Judgment Based on Obviousness Because All Four *Graham* Factors Are in Material Dispute

A claimed invention is only deemed obvious "if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 662 (Fed. Cir. 2000) (quoting 35 U.S.C. § 103(a)). "The obviousness determination turns on underlying *factual* inquiries involving: (1) the scope and content of prior art, (2) differences between claims and prior art, (3) the level of ordinary skill in pertinent art, and (4) secondary considerations such as commercial success and satisfaction of a long-felt need." *Proctor & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (emphasis added) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)). Summary judgment is only

appropriate where these *Graham* factors "are not in material dispute." *KSR Int'l. Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007); *see also Commonwealth Scientific & Indus. Research Org. v. Buffalo Tech. (USA), Inc.*, 542 F.3d 1363, 1375-77 (Fed. Cir. 2008) (holding that fact issues respecting the *Graham* factors precluded summary judgment). Here, as demonstrated below, all four *Graham* factors are in material dispute. Accordingly, summary judgment is grossly inappropriate. *See Novartis Pharm. Corp.*, 2009 WL 483865, at *3 (Cavanaugh, J.) (denying summary judgment motion because "genuine issues of fact exist with respect to the scope, content and teaching of the prior art, differences between the prior art and the . . . patent, and secondary considerations such as failures of others, unexpected properties and commercial success").

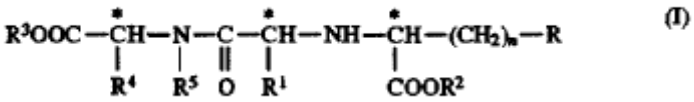
Moreover, "[b]ecause patents are presumed to be valid, *see* 35 U.S.C. § 282, an alleged infringer seeking to invalidate a patent on obviousness grounds must establish its obviousness by facts supported by clear and convincing evidence." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006). In particular, the alleged infringer "must demonstrate 'by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have a reasonable expectation of success in doing so.'" *Proctor & Gamble Co.*, 566 F.3d at 994 (citation omitted). Here, as shown below, Glenmark has utterly failed to carry its burden.

II. Glenmark Is Wrong About the Level of Ordinary Skill in the Art

As an initial matter, a material dispute exists as to what constitutes the level of ordinary skill in the art pertaining to the '244 patent. The art related to the '244 patent is multi-disciplined. (Pls.' Stmt.¶ 14.) It involves medicinal chemistry, organic chemistry, pharmacology and cardiovascular medicine. (*Id.*) Accordingly, a person of ordinary skill in the

art pertaining to the '244 patent would necessarily include people who are skilled in those different aspects of the '244 patent. (*Id.*)

Glenmark's expert, Dr. Rosendorff, who is a medical doctor and not a chemist, however, opines that a person of ordinary skill is limited to a pharmacologist or medical professional involved in the research and development of therapies for hypertension. (Rosendorff Decl. ¶ 27.) But even a cursory review of the '244 patent and its claims reveals that Glenmark is wrong. The '244 patent discloses and claims, *inter alia*, a pharmaceutical composition comprising an ACE inhibitor having certain heterocyclic bicyclic or tricyclic ring systems of the chemical formula I below and a calcium antagonist in amounts effective to treat hypertension.



Without knowledge of chemistry, one would be unable to ascertain the scope of the claims of the '244 patent. (Pls.' Stmt. ¶ 17.) This is underscored by Dr. Rosendorff's inability to understand the scope of claim 1. He could not determine how many compounds were covered by claim 1 of the '244 patent. (*Id.* ¶ 18.) He admitted that he did not know whether any of the claimed compounds having the bicyclic or tricyclic ring system were known as of October 1986 because the list of the bicyclic or tricyclic radicals described in the '244 patent was "incredibly complex." (Pls.' Stmt. ¶ 18.) He also acknowledged that a person of ordinary skill under his definition would not be able to synthesize many of the compounds covered by claim 1 of the '244 patent. (*Id.*) Finally, Dr. Rosendorff conceded that he did not even understand the chemical structures of the various ACE inhibitors at issue -- captopril, enalapril, and quinapril. (*Id.* ¶ 66.)

The education level of the inventors also shows that the level of ordinary skill required knowledge in chemistry. *See Ruiz*, 234 F.3d at 666-67 (listing "the educational level of active workers in the field" as a factor in determining the level of ordinary skill in the art). Here, four of the five inventors of the '244 patent were chemists. (Pls.' Stmt. ¶ 16.) Accordingly, a person having ordinary skill in the art would have to include an organic or a medicinal chemist. (*Id.* ¶ 19.)

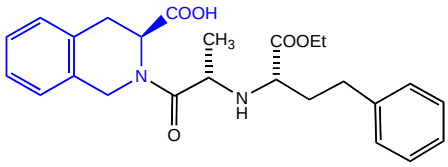
Since Glenmark's allegation of obviousness is based solely upon Dr. Rosendorff's erroneous definition of the level of ordinary skill, this dispute on the level of ordinary skill alone justifies denial of Glenmark's summary judgment motion. *See Fisher-Barton Blades, Inc. v. Blount, Inc.*, 584 F.Supp.2d 1126, 1152 (E.D. Wis. 2008) (factual dispute as to level of ordinary skill in the art precluded summary judgment).

III. The Asserted Claims of the '244 Patent Are Not Obvious Over Prior Art Combinations of Captopril, Enalapril, or Lisinopril with a Calcium Antagonist

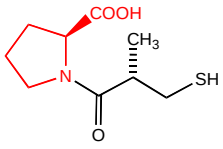
Glenmark's obviousness argument relies on a combination of at least *eleven* prior art references. But none of these references, nor the state of the art at the time, provided any motivation or reason for one of ordinary skill to substitute quinapril in the disclosed combinations of enalapril, captopril, or lisinopril with a calcium antagonist to create a pharmaceutical composition effective for treating hypertension. (*See* Pls.' Stmt. ¶¶ 44-84.) Worse yet, Glenmark misconstrues the scope and content of the prior art, ignores critical differences between the prior art and the invention of the '244 patent, glosses over critical claim limitations, and misapplies the law governing obviousness.

A. Glenmark Ignores Significant Structural Differences Between Quinapril and Captopril, Enalapril, and Lisinopril

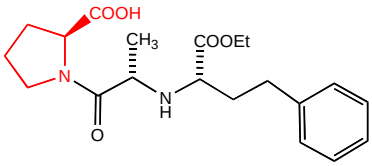
Glenmark relies on prior art combinations of captopril, enalapril, or lisinopril[3] with a calcium antagonist to support its allegation of obviousness. However, Glenmark completely ignores the fact that these compounds are structurally significantly different from quinapril. (*See* Pls.' Stmt. ¶¶ 20-32, 37.) The structures of these compounds are illustrated below:



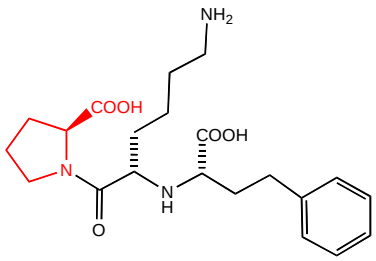
QUINAPRIL



CAPTOPRIL



ENALAPRIL



LISINOPRIL

The structural differences between enalapril, lisinopril, and captopril and quinapril give rise to meaningful differences in physical and biological properties, including hydrophobicity and hydrophilicity, molecular weight, critical volume, electron density distribution and dimensions. (Pls.' Stmt. ¶¶ 34-36.) In particular, these differences in properties arise because, among other structural differences, monocyclic (such as the proline ring (shown in red above) in captopril, enalapril, and lisinopril) and bicyclic (such as the tetrahydroisoquinoline ring (shown in blue above) in quinapril) ring systems have different 3-dimensional shapes. (*Id.* ¶

[3] Glenmark raised for the first time in its summary judgment motion the argument that a combination of quinapril with a calcium antagonist would have been obvious to a person of ordinary skill in the art over the lisinopril and CCB combination suggested in a prior art reference (Garthoff).

34.) One of ordinary skill would have understood that these significant structural, physical and biological differences affect the physicochemical, pharmacokinetic, and pharmacological properties of the compounds, and as a result one would not have been able to predict reasonably how these differences could affect the activity of the ACE inhibitor compounds in any combination with a calcium antagonist. (*Id.* ¶ 38.)

Moreover, as of October 1986, neither the structure of ACE (the target enzyme in the human body) nor the mechanism of action of ACE inhibitors was known. (Pls.' Stmt. ¶¶ 104-08.) Further, contrary to Glenmark's assertion, it was not known whether calcium antagonists and ACE inhibitors acted in independent ways to regulate blood pressure -- a fact that Dr. Rosendorff himself acknowledged. (*Id.* ¶ 111.) These facts lent further unpredictability to one having ordinary skill in the art in devising any pharmaceutical composition containing an ACE inhibitor and a calcium antagonist.

As the Federal Circuit has recognized, "chemical arts are often" "unpredictable" and present a "difficult hurdle" for finding predictable solutions, particularly in light of "*KSR*'s focus on these 'identified, predictable solutions.'" *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). Here, given the unpredictability in both biological and physical properties resulting from the structural differences between quinapril and the other ACE inhibitors and the fact that the ACE structure and ACE inhibition mechanism were not even known at the time of the invention, one of ordinary skill -- even knowing that a compound with a monocyclic ring system, such as captopril, enalapril, or lisinopril, had some ACE inhibiting activity and may have had some effect in lowering blood pressure in combination with a calcium antagonist -- would not have substituted quinapril for captopril, enalapril, or lisinopril in such combinations. (Pls.' Stmt. ¶¶ 38-39, 109.) Indeed, Glenmark failed to cite a single piece of prior

art that disclosed a combination of any ACE inhibitor having a bicyclic ring system and a calcium antagonist.

Contrary to Dr. Rosendorff's assertion (Rosendorff Decl. ¶ 45), a person of ordinary skill would have been concerned about structural differences among different ACE inhibitors in devising any pharmaceutical composition containing an ACE inhibitor and a calcium antagonist. (Pls.' Stmt. ¶ 33.) In fact, the PTO rejected Dr. Rosendorff's position. The PTO examiner allowed the claims of the '244 patent on the ground that the structural differences between enalapril and the bicyclic compounds claimed by the '244 patent, which included quinapril, rendered the claimed invention non-obvious over what Glenmark acknowledges to be the closest prior art -- the Garthoff patent disclosing a combination of enalapril with a calcium antagonist. (*Id.* ¶ 42.)

Given the PTO's position and plaintiffs' experts' explanation of the importance of structural differences (*id.* ¶¶ 33-42), it is not surprising that even Dr. Rosendorff himself considered the chemical structures of ACE inhibitors in determining what constitutes the closest prior art to the '244 patent. (Rosendorff Decl. ¶ 37.) Specifically, he stated that the enalapril/calcium antagonist "combinations are closer than the captopril/calcium antagonist combinations because quinapril and trandolapril *are closer to enalapril in structure and properties* than they are to captopril." (*Id.*) (Emphasis added.) Glenmark cannot have it both ways, arguing that a person of ordinary skill would not have been concerned about structural differences and yet asserting that structural differences need to be considered in assessing what constitutes the closest prior art.

This factual dispute -- whether a person of ordinary skill would have considered structural differences between quinapril and the prior art ACE inhibitors -- is both genuine and material and is yet another reason Glenmark's summary judgment motion should be denied.

B. Glenmark Ignores Critical Claim Limitations

Glenmark did not even attempt to construe key claim limitations in the '244 patent, i.e., "pharmaceutical composition" and "in amounts effective for treating hypertension." As will be shown below, Glenmark's obviousness arguments fail miserably because when properly construed, the prior art references relied upon by Glenmark fail to meet these limitations.

1. Meaning of "Pharmaceutical Composition"

Claim 1 of the '244 patent recites a "pharmaceutical composition" comprising (a) an ACE inhibitor having the chemical formula (I), which includes quinapril, and (b) a calcium antagonist, wherein the ACE inhibitor and the calcium antagonist are present in the composition "in amounts effective for treating hypertension." (Pls.' Stmt. ¶ 3.) The '244 patent describes a "pharmaceutical composition" as one that "can be prepared, for example, by intimately mixing the single components as powders, or by dissolving the single components in a suitable solvent such as, for example, a lower alcohol and then removing the solvent." (*Id.* ¶ 5.) Thus, a "pharmaceutical composition" means a combination of two substances that are mixed or dissolved together, for example, in a fixed dose of each forming a single dosage form. (*Id.*) Dr. Rosendorff ostensibly agrees with plaintiffs' interpretation, stating that "pharmaceutical composition" means that the drug substances are combined in "one formulation," i.e., "in one tablet or capsule." (*Id.* ¶ 6.) Glenmark further admits that the "pharmaceutical composition" disclosed and claimed in the '244 patent is a "drug product." (*Id.*)

2. Meaning of "In Amounts Effective for Treating Hypertension"

Hypertension is a life-long disease, in which chronic high blood pressure is the primary measure, requiring daily administration of medication. (Pls. Stmt. ¶ 7.) As such, a pharmaceutical composition comprising the claimed ACE inhibitor and calcium antagonist "in amounts effective for treating hypertension" means that the drug product should be effective in reducing chronic high blood pressure and maintaining its efficacy over the course of months and years.[4] (*Id.*) Dr. Rosendorff concedes this point. He testified that "in almost all patients, once hypertension has been developed, it will continue for the rest of that patient's life" because hypertension "is a chronic disease." (*Id.* ¶ 8.) He added that "[i]n nearly all cases, it will be necessary for patients to start anti-hypertensive therapy and continue that lifelong." (*Id.*)

C. Glenmark Misconstrues the Scope and Content of the Prior Art

1. The Captopril References

None of the references cited by Glenmark, Stornello, MacGregor, Brouwer, Mimran, Zanchetti and White, "collectively and individually disclose the essential concept of the '244 patent: combine an ACE inhibitor and a calcium antagonist to treat hypertension." (Glenmark Br.[5] 8.) First, none of these references disclose captopril and a CCB in a "pharmaceutical composition" as required by the claims of the '244 patent -- *i.e.*, combined in "one formulation," such as "in one tablet or capsule." (Pls.' Stmt. ¶ 6.) Dr. Rosendorff concedes that each of these references discloses administering captopril and a calcium antagonist in

[4] Contrary to Glenmark's assertion, the '244 patent provides examples of pharmaceutical compositions with effective amounts of an ACE inhibitor and a calcium antagonist to treat hypertension. (Pls. Stmt. ¶ 7.)

[5] "Glenmark Br." refers to Defendants Glenmark Pharmaceuticals Inc. USA and Glenmark Pharmaceuticals Ltd.'s Memorandum in Support of Their Motion for Summary Judgment That Claims 1-4, 7 and 10 of U.S. Patent 5,721,244 Are Invalid.

separate doses. (*Id.* ¶ 49.) Therefore, even if one were to substitute quinapril for captopril in the combinations described in these references, the resulting combinations would not be in a pharmaceutical composition.

Second, none of these references support the use of the combinations for the treatment of hypertension. (*Id*. ¶¶ 51-53, 59.) Stornello, MacGregor, Brouwer, Mimran, and White were all based on clinical studies conducted with extremely small patient populations, flawed and varied methodologies, and no statistical validation. (*Id.* ¶¶ 51-52.) Accordingly, a person of ordinary skill in the art would not be able to draw any reliable conclusion from these results. (*Id.* ¶ 53.) At best, given the limitations and flaws in these studies, a person of ordinary skill may have attempted to use the *same* captopril and CCB combinations (administered in separate doses) in better designed studies to fully elucidate their blood pressure lowering effects. (*Id.*) Indeed, the White reference confirms this fact, noting that "*the long term efficacy* of the captopril and nifedipine combination [tested therein] should be evaluated." (*Id.* ¶ 55.) (Emphasis added.) Contrary to Glenmark's assertion (*see* Rosendorff Decl. ¶ 15), there is no evidence that researchers ever recognized combining captopril and CCB in a pharmaceutical composition. Indeed, no captopril and CCB combination has ever been marketed for the treatment of hypertension. (*Id.*)

Finally, at the time of the invention in October 1986, captopril was understood to be a first generation ACE inhibitor with limited clinical utility. It was known to have a short half-life, which required that it be administered two or three times per day for treating hypertension. (Pls.' Stmt. ¶ 46.) Moreover, captopril was known to have adverse side effects. (*Id.*) Given captopril's properties and significant structural differences from quinapril (*see supra*

at 9-10), one of ordinary skill would not have considered quinapril to be interchangeable with captopril. (*Id.* ¶ 21.)

In sum, none of the captopril references would have led one of ordinary skill to substitute quinapril for captopril with the reasonable expectation that the resulting combination would be successful for treating hypertension. (*Id.* ¶ 59.)

2. The Enalapril and Lisinopril References

The enalapril and calcium antagonist combinations of Garthoff and Vincent relied on by Glenmark would not have motivated or given any reason to a person of ordinary skill in the art in October 1986 to substitute quinapril for enalapril or lisinopril in any prior art combination with a calcium antagonist. (Pls.' Stmt. ¶¶ 60-77.)

First, Garthoff, which Glenmark acknowledges to be the closest prior art (*see* Glenmark's Stmt.[6] ¶ 57), was considered by the patent examiner during prosecution of the '244 patent. Thus, Glenmark's burden to demonstrate obviousness is made "especially difficult." *See Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990).

Garthoff fails to teach or suggest a pharmaceutical composition that was effective for treating hypertension, as required by the claims of the '244 patent. Garthoff discloses a combination of enalapril or lisinopril with a calcium antagonist such as nitrendipine, nisoldipine, nicardipine or felodipine. (Pls.' Stmt. ¶ 63.) But Garthoff provides pharmacological data only for the enalapril and nitrendipine combination. (*Id.*) There is no pharmacological data for any lisinopril combination. (*Id.*)

[6] "Glenmark's Stmt." refers to Defendants Glenmark Pharmaceuticals Inc., USA and Glenmark Pharmaceuticals Ltd.'s Statement of Material Facts Not In Dispute In Support of Their Motion for Summary Judgment that Claims 1-4, 7 and 10 of U.S. Patent 5,721,244 Are Invalid

In Garthoff, hypertension in rats was artificially induced and blood pressure was then measured following administration of enalapril and nitrendipine. (Pls.' Stmt. ¶ 67.) Although blood pressure was said to have been recorded for over 24 hours, Garthoff provides data only for nine hours. (*Id.*) The data in Garthoff show that the blood pressure lowering effects of the enalapril and nitrendipine combinations reached their peak at about 30 minutes after administration and then leveled off at about nine hours. (*Id.* ¶ 69.) Therefore, Garthoff describes only an acute or short-term test for measuring blood pressure and does not disclose efficacy in treating hypertension. (*Id.* ¶ 68.)

As Garthoff disclosed only an acute blood pressure lowering effect, it would not have taught or suggested to one having ordinary skill that its combinations would have been effective for treating hypertension, as required by the claims of the '244 patent. Even Dr. Rosendorff agrees with this fact:

> Q. Do the data in Garthoff show that enalapril/nitrendipine combination will be effective in treating hypertension?
>
> A. Well, one certainly wouldn't treat hypertension with that combination just on the basis of these data alone.

(Pls.' Stmt. ¶ 69.) Moreover, the data in Garthoff did not show that the combination performed any better than enalapril alone. Administration of the enalapril and nitrendipine combination reduced blood pressure more than enalapril only for about a two hour period. (*Id.* ¶ 70.) Further, the data in Garthoff are of questionable utility because they were not analyzed for statistical validity. (*Id.*) There is also no indication in Garthoff that the test animals were administered enalapril in a pharmaceutical composition with nitrendipine. (*Id.*)

Vincent, the other enalapril-related reference put forward by Glenmark, also fails to teach or suggest a pharmaceutical composition that was effective for treating hypertension, as required by the claims of the '244 patent. Vincent tested blood pressure lowering effects of

enalapril and nifedipine (a calcium antagonist) in spontaneously hypertensive rats, but it neither disclosed nor suggested that these compounds were administered together in a "pharmaceutical composition." (Pls.' Stmt. ¶ 71.) In fact, these compounds were not even administered at the same time. Rather, nifedipine was administered in a separate formulation one hour after administration of enalapril. (*Id.*)

Vincent's data did not establish that the administration of enalapril followed by nifedipine was effective for treating hypertension. Vincent provided blood pressure data for the enalapril and nifedipine combination over a period of only seven hours. (*Id.* ¶ 73.) Thus, like Garthoff, it disclosed an acute test for measuring blood pressure. (*Id.*) The data provided in Vincent showed that after seven hours, the blood pressure of the enalapril and nifedipine group was only slightly lower than that of enalapril alone. (*Id.* ¶ 74.) Accordingly, Vincent noted that "additivity could not be clearly established at these maximally effective doses." (*Id.*) Indeed, Dr. Rosendorff acknowledges that the data in Vincent did not establish that a combination of enalapril and nifedipine could be used to maintain sustained low blood pressure at a level below hypertension. (*Id.* ¶ 75.) As Vincent disclosed only the short term blood pressure lowering effect of enalapril and nifedipine, it would not have taught or suggested to one of ordinary skill that this combination would have been effective for treating hypertension, as required by the claims of the '244 patent. (*Id.*)

In sum, the acute rat studies in Vincent and Garthoff showed that their drug combinations lowered blood pressure over, at best, a few hours -- insufficient for treating hypertension. (Pls' Stmt. ¶ 76.) They did not provide any information about the long term efficacy of these combinations or how they would perform in a chronic setting. Consequently, neither Vincent nor Garthoff demonstrated that combinations of enalapril or lisinopril with a

calcium antagonist would be effective for treating hypertension, as is required by the claims of the '244 patent. (*Id.*) Accordingly, neither reference would have led one of ordinary skill to substitute quinapril for enalapril or lisinopril with the reasonable expectation that the resulting combination would be successful for treating hypertension. (*Id.* ¶ 77.)

3. The Quinapril References

The Kaplan, Ryan, and Gavras references relied upon by Glenmark would not have motivated or provided any reason to one of ordinary skill in the art to substitute quinapril for captopril, enalapril or lisinopril in an ACE inhibitor and calcium antagonist combination. First, none of these references disclosed or suggested using quinapril in combination with a calcium antagonist. (Pls.' Stmt. ¶ 79.) In each reference, quinapril was tested by itself.

Second, all three studies were acute and did not demonstrate quinapril's ability to treat hypertension -- a chronic condition requiring long term treatment. (Pls' Stmt. ¶ 81.) The Gavras study lasted only 48 hours. (*Id.*) Kaplan and Ryan tested the ACE inhibition response of quinapril in rats and dogs from four hours to at most five days. (*Id.*) The Gavras study was also flawed. It was an exceedingly small study involving only eight patients -- too small for statistical validation. (*Id.* ¶ 83.) In addition, it was not randomized, controlled, or double-blinded. (*Id.*)

Third, all three studies showed that quinapril was at best equipotent to enalapril and not clearly better than captopril. (*Id.* ¶ 80.) To the extent Glenmark claims that Kaplan and Ryan "showed that quinapril had excellent activity compared to both enalapril and captopril" (Glenmark's Stmt. ¶ 46) or that it was "considerably more potent" than enalapril or captopril (Glenmark Br. at 11), it is incorrect. Dr. Rosendorff himself pointed out that the Ryan study showed that quinapril had "approximately the same activity as enalapril" and the Gavras study showed that quinapril was equipotent to enalapril. (Pls.' Stmt. ¶ 80.)

Given that the studies on quinapril as a single compound did not demonstrate that it was effective for treating hypertension, and that quinapril was at best equipotent to enalapril and not clearly better than captopril, one of ordinary skill would have no reason to substitute quinapril for enalapril, captopril or lisinopril in any prior art combination with a calcium antagonist. Moreover, because the studies on the existing combinations of enalapril or captopril with a calcium antagonist did not show that such combinations were effective for treating hypertension (and there were no such studies on any lisinopril combinations), one of ordinary skill would have had no reasonable expectation that the resulting combinations would be effective in treating hypertension.[7] (Pls.' Stmt. ¶ 81.)

D. One of Ordinary Skill Would Not Have Selected Quinapril in Developing Any Pharmaceutical Composition with a Calcium Antagonist

Even aside from the deficiencies in the references relied upon by Glenmark, a person of ordinary skill in the art would not have selected quinapril in developing any pharmaceutical composition with a calcium antagonist. This case does not present "a situation with a finite, and in the context of the art, small or easily traversed, number of options that would convince an ordinary skilled artisan of obviousness." *See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008). In *Ortho-McNeil*, the court held the patent in suit non-obvious because there was a myriad of options available and one of ordinary skill would have no "reason to select (among several unpredictable alternatives) the exact route that produced [the invention]." *Id.*; *see also Eisai Co.*, 533 F.3d at 1359 ("[A] prima facie case of

[7] Glenmark states that the "effective amounts" of many ACE inhibitors and calcium antagonists were well established, and were known to persons skilled in the art. (Glenmark Br. at 4). This is incorrect. None of the prior art references relied upon by Glenmark, nor the state of the art, showed the effective amounts of any pharmaceutical composition for treating hypertension because, as discussed herein, nothing in the prior art taught or suggested a pharmaceutical composition effective for the treatment of hypertension.

obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound.").

Similarly here, at the time of the invention, the literature showed that there were conservatively at least 297 compounds known to have ACE inhibiting activity greater than, about equivalent to, or within an order of magnitude of the ACE inhibiting activity of enalapril or captopril. (Pls.' Stmt. ¶ 85.) A person of ordinary skill would have no reason to select quinapril as the lead or one of the lead compounds from this large group of ACE inhibitors for further development in any combination with a calcium antagonist for treating hypertension. (*Id.* ¶ 86.)

Further, given the limitations and unpredictability in carrying out testing in animals and clinical human trials, one of ordinary skill could not test, and would not have tested, all of the at least 297 compounds to see whether when combined with a calcium antagonist, the resulting combinations would have sufficient activity to treat hypertension. **(**Pls.' Stmt. ¶ 87.) Instead, a person of ordinary skill would be more likely to have chosen one or more compounds which have structures closer to enalapril or captopril, *i.e.*, compounds with a monocyclic proline ring, such as lisinopril, since enalapril and captopril were known to have some blood pressure lowering activity when combined with a calcium antagonist. (*Id.* ¶ 87.) And the literature showed that there were at least 109 such compounds. (*Id.*) Accordingly, as of October 1986, a person of ordinary skill in the art would have no reason to select, and would not have selected, quinapril for combining with a calcium antagonist. (*Id.* ¶ 88.)

E. ACE Inhibitors Are Not Interchangeable or Alike

Glenmark suggests that all ACE inhibitors belong to the same class and thus it would have been obvious to substitute another known ACE inhibitor instead of enalapril, captopril or lisinopril in the prior art combinations cited by Glenmark. (*See* Glenmark Br. 8, 16.)

Contrary to Glenmark's assertion, none of the references cited by Glenmark suggested that any ACE inhibitor could be combined with a calcium antagonist. (*See* Pls.' Stmt. ¶ 56.)[8]

First, Glenmark is wrong in relying on the Zanchetti, Vincent, and Garthoff articles to show an alleged "class" effect. Zanchetti did not refer to a class of ACE inhibitors that included quinapril, nor did it suggest that ACE inhibitors were all the same. (*Id.*) The discussion of ACE inhibitors in Zanchetti was limited to only captopril and enalapril. The references Zanchetti cited about ACE inhibitors -- Mimran and Brouwer -- disclosed only administering captopril and a CCB in *separate* doses. (*Id.* ¶ 50.) Indeed, Dr. Rosendorff conceded that Zanchetti did not show that ACE inhibitors had a "class" effect. (*Id.* ¶ 56.) In responding to the question, "[d]oes Zanchetti have any data or studies showing that all ACE inhibitors are alike," he conceded: "No, there are no data in this paper at all. . . ." (*Id.*)

Likewise, Vincent did not suggest the use of any compound within a "class" of ACE inhibitors. (Glenmark's Br. 16.) Dr. Rosendorff agreed that the observations in Vincent could not be extrapolated to other ACE inhibitors. He explicitly conceded that Vincent said nothing about ACE inhibitors other than enalapril:

> Q. So there's no description of any ACE inhibitor other than enalapril in Vincent; is that correct?
>
> A. Correct.

(Pls.' Stmt. ¶ 72.) Indeed, Glenmark admits that as of October 1986, there were only two ACE inhibitors approved for the treatment of hypertension – captopril and enalapril. (*Id.* ¶ 57.)

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[8] Plaintiffs did not admit "that the idea of combining ACE inhibitors and calcium antagonists for the treatment of hypertension was known in the art," as alleged by Glenmark. (Glenmark Br. at 16.) The only prior art combination identified in the '244 patent is a combination of enalapril and a calcium antagonist. (Rosendorff Decl. Ex. 1, col. 1, ll. 46-48.)

Further, contrary to Dr. Rosendorff's assertion, Garthoff did not "recognize[] that essentially any member of the entire class of ACE inhibitors could be combined with a calcium antagonist." (Pls.' Stmt. ¶ 64.) The Garthoff generic formula includes only certain ACE inhibitors with a monocyclic ring, such as proline, which is not present in quinapril. (*Id.*)[9] The PTO recognized this essential difference when it allowed the claims of the '244 patent. (*See id.* ¶¶ 41-43.)

Moreover, as explained in detail by plaintiffs' experts, there were known significant differences among ACE inhibitors which impact their properties, including the degree to which they reduce blood pressure. (Pls.' Stmt. ¶ 89.) In addition to having different chemical structures and potencies, ACE inhibitors also differ in their prodrug status, tissue ACE activity including lipophilicity and tissue binding, route of elimination, trough-peak ratios, adverse events and drug interactions, which affect their pharmacokinetic and pharmacodynamic properties. (*Id.* ¶¶ 92-99.) Indeed, Dr. Rosendorff agrees that ACE inhibitors have different durations of action. (*Id.* ¶ 91.) He further stated in two published and peer reviewed articles that all ACE inhibitors are not alike. (*Id.* ¶ 90.)

F. The State of the Art Did Not Recommend Using Pharmaceutical Compositions Containing ACE Inhibitors and Calcium Antagonists for the Treatment of Hypertension as of October 1986

Pharmaceutical compositions containing an ACE inhibitor and a CCB were not employed by physicians for treating hypertension at the time of invention in October 1986. (Pls.' Stmt. ¶¶ 112-22.) By October 1986, only a stepped-care approach, which involved giving

[9] Moreover, Dr. Rosendorff is not even qualified to make this assertion as he did not review the generic formula in Garthoff, nor did he investigate whether that formula covered quinapril or trandolapril. (Pls.' Stmt. ¶ 65.) This is not surprising since Dr. Rosendorff, who is not a chemist, did not even understand the chemical structures of captopril, enalapril, or quinapril. (*Id.* ¶ 66.)

patients separate doses of antihypertensive agents, was the recommended and accepted method of treatment for hypertension. Pharmaceutical compositions containing an ACE inhibitor and a CCB did not become the recommended method of treatment until 1997, ten years later. (*Id.* ¶ 120.) This further supports the non-obviousness of the claimed pharmaceutical composition.

Further, as Dr. Rosendorff stated, quinapril was not approved in the U.S. until 1991.[10] (*Id.* ¶ 123.) A practicing physician would not have substituted an unapproved drug for captopril or enalapril (both of which were approved by October 1986) to treat hypertension. (*Id.*) Dr. Rosendorff, himself a physician, agreed that a doctor would not prescribe a drug that was not approved by the FDA. (*Id.*)

G. The Claimed Invention Exhibits Unexpected Results

Secondary considerations such as unexpected results and commercial success also demonstrate that the claimed invention was not obvious. Secondary considerations are "essential components of the obviousness determination." *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). "This objective evidence of nonobviousness includes copying, long felt but unsolved need, failure of others, commercial success, unexpected results created by the claimed invention, unexpected properties of the claimed invention, licenses showing industry respect for the invention, and skepticism of skilled artisans before the invention." *Id.* (citations omitted).

Glenmark argues that plaintiffs have not shown that the claimed invention is unexpectedly superior to the closest prior art combination, namely enalapril and a calcium

[10] Glenmark's premise that the invention of the '244 patent is simply a combination of "two old drugs" (Glenmark Br. at 2) is not only incorrect, it is contradicted by Glenmark's own admissions that quinapril was approved as a drug only in 1991, five years after the invention of the '244 patent. Further, there is no evidence that at the time of the invention calcium antagonists were approved as drugs for treating hypertension.

antagonist. (Glenmark Br. 22.) This is false.[11] Tarka® (a combination of the ACE inhibitor trandolapril and the calcium antagonist verapamil falling within the scope of the claims) has an unexpectedly longer duration of action than the prior art enalapril and calcium antagonist combinations. Tarka® has been shown to have efficacy over 24 hours. (Pls.' Stmt. ¶ 131.) In contrast, a combination of an enalapril with a calcium antagonist did not exhibit such efficacy. (*Id.*. ¶ 132.) Moreover, while Tarka® is a once a day drug, both Lexxel® and Teczem®, which are enalapril and calcium antagonist combination drugs, require twice a day dosing in some patients. (*Id.* ¶ 129.)

The Federal Circuit has further recognized that unexpected results of a combination product can be demonstrated by showing that the combination has surprisingly better properties than those of the individual components. *Knoll Pharm. Co. v. Teva Pharm. USA*, Inc., 367 F.3d 1381, 1384-85 (Fed. Cir. 2004). Here, Tarka® has demonstrated a dramatic ability to reduce blood pressure as compared to its individual components. In some cases, Tarka®'s blood pressure reducing ability has been shown to be "superadditive," *i.e.*, more than the sum of its parts. (Pls.' Stmt. ¶ 134.) Tarka®'s superadditive blood pressure reduction is a surprising and unexpected result. (*Id.* ¶ 133.) In contrast, studies of combinations of captopril or enalapril with a calcium antagonist have shown that the ability of those combinations to lower blood pressure *is less* than the sum of the effect of their individual components. By October 1986, it was reported that a combination of captopril and nifedipine (a CCB) had "no significant additive effect on blood pressure." (*Id.* ¶ 137.) Moreover, as discussed above, the results in

[11] Glenmark also argues that plaintiffs have not cited any data showing any property of a combination of quinapril with a calcium antagonist. However, quinapril and trandolapril are both bicyclic compounds and as recognized by Dr. Rosendorff they "are closer" in structure and properties. (Pls.' Stmt. ¶ 40.)

Vincent did not establish that the blood pressure lowering effect of enalapril and nifedipine was additive as compared to administration of the individual agents.

Tarka® has also been shown to have a sustained and marked antihypertensive effect in black patients. In a study in which black patients with mild to moderate hypertension were treated with Tarka®, the authors concluded that "the combination exerted a profound antihypertensive effect." (Pls.' Stmt. ¶ 141.) They also concluded that "it is reasonable to suggest" that Tarka® was "synergistic in these hypertensive patients." (*Id.*) Glenmark has not pointed to any study showing that an enalapril and calcium antagonist combination is effective in treating hypertension in black patients. Indeed, Dr. Rosendorff's own paper suggests that enalapril is not effective in black patients. (*Id.* ¶ 142.)

Tarka® exhibits numerous other unexpected properties, including synergistically improving blood vessel structure and function, reducing the incidence of cardiac events, reducing proteinuria to a greater extent than trandolapril and verapamil monotherapy, and delaying the onset of diabetes and exhibits glycemic neutrality. (*Id.*. ¶¶ 143-56.) Tarka®'s properties are not simply the expected effects of its component parts, but are enhanced by the combination of trandolapril and the calcium antagonist. (*Id.* ¶ 140.)

H. Tarka® Is a Commercial Success

The "commercial response to an invention is significant to a determination of obviousness, and is entitled to fair weight." *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.* 851 F.2d 1387, 1391 (Fed. Cir. 1988). Indeed, "[w]hen a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention." *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). Moreover, market acquiescence is evidence of non-obviousness. *RCA Corp. v.*

Applied Digital Data Sys., Inc., 730 F.2d 1440, 1448 (Fed. Cir. 1984) (patent not obvious where "commercial acquiescence of competitors [was] evidenced by . . . extensive licensing of invention"); *In re Sernaker*, 702 F.2d 989, 996 (Fed. Cir. 1983) (non-obviousness evidenced by the "fact that [though] a patent has not yet issued . . . appellant has been able to license his invention . . . [and] licensees have sold millions" of the invention).

Here, Tarka® is not only commercially successful, but has been significantly more successful than what Glenmark acknowledges to be the closest prior art combinations. First, Abbott invested in Tarka® by paying Aventis Pharma S.A. [redacted] to obtain the exclusive right to make and market Tarka® under the '244 patent. (Pls.' Stmt. ¶ 158.) This is strong evidence of commercial acquiescence. Further, Tarka®'s net annual sales have increased from [redacted] when it was launched in 2000 to [redacted] in 2008. (*Id.* ¶ 157.) Despite the fact that [redacted], the net annual sales of Tarka® actually went up, from [redacted] in 2006 to [redacted] in 2007. (*Id.*)

Merck & Co. v. Teva Pharms. USA, Inc., 395 F.3d 1364 (Fed. Cir. 2005), cited by Glenmark, is inapplicable. (Glenmark Br. 24.) There, the court found no commercial success because another patent precluded competitors from marketing the prior art method. *Id.* at 1377. Here, the enalapril and calcium antagonist combinations of the closest prior art had been marketed, but they were utter commercial failures. Lexxel®, which is a product containing enalapril and felodipine (a combination specifically disclosed in Garthoff), was launched in 1997, but by June 2004 its sales were only $2 million and by 2005 its market share was *zero*. (Pls.' Stmt. ¶ 159.) Teczem®, which is a product containing enalapril and diltiazem (a calcium antagonist), was launched in 1996, but had *zero* sales by June 2004, and was discontinued in

2006. (*Id.*) Further, there is no evidence that a drug product containing a combination of captopril or lisinopril with a calcium antagonist has ever been marketed. The fact that Tarka® is much more commercially successful than the closest prior art combinations is strong evidence that the invention of the '244 patent was not obvious.

Glenmark argues that Tarka®'s commercial success cannot be attributed to the '244 patent because Tarka® was protected by another patent (the '361 patent) which allegedly prevented competition. (*See* Glenmark Br. 23-24.) This argument is flawed. The '361 patent expired on June 12, 2007. But since then Tarka® has grossed over [redacted] in sales. (Pls.' Stmt. ¶ 157.) These sales can only be attributed to the '244 patent.

I. Glenmark Seeks to Copy Tarka®

As a result of Tarka®'s success, Glenmark now wants to make a copycat Tarka® product. Dr. Soni, Glenmark's 30(b)(6) witness, agreed that the level of sales of Tarka® induced Glenmark to make a copycat version of it. (Pls.' Stmt. ¶ 158.) Glenmark's copying further confirms the success and non-obviousness of the invention of the '244 patent. *See Pfizer Inc. v. Ranbaxy Labs. Ltd.*, 405 F. Supp. 2d 495, 518 (D. Del. 2005) (non-obviousness based in part on evidence of copying), *rev'd on other grounds*, 457 F.3d 1284 (Fed. Cir. 2006); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 759 (N.D. W. Va. 2004) (same).

IV. Glenmark Misapplies the Law

Glenmark's reliance on *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476 (Fed. Cir. 1997) is grossly misplaced. *Richardson-Vicks* was not decided on summary judgment, but after a jury trial on the merits, applying the standard of "assess[ing] the record evidence in the light most favorable to the verdict winner." *Id*. at 1477. This standard does not apply to the instant case at summary judgment. Furthermore, the facts of *Richardson-Vicks* present a situation highly unlike the present case. There, the patent at issue claimed, *inter alia*, a

"combinatory immixture" of two substances, ibuprofen and pseudoephedrine. The court held the patent obvious because before the date of the invention the prior art already disclosed the *exact* combination claimed by the patent. As the trial evidence showed, it was already known that "ibuprofen was prescribed in combination with pseudoephedrine by the doctors," that the "only difference between the prescribed combination and the patented invention is that the prescription was not contained in a single tablet," and the prior art suggested mixing these two substances. *Id*. at 1480, 1483-84. Indeed, the evidence showed that before the invention, another party had already combined ibuprofen and pseudoephedrine in a mixture. *Id*. at 1484. In stark contrast, in the present case, there is nothing in the prior art that disclosed or suggested the claimed composition of quinapril with a calcium antagonist.

Much more pertinent to the instant case are *Knoll Pharmaceutical Co.*, 367 F.3d 1381 and *Ortho-McNeil Pharmaceutical, Inc. v. Teva Pharmaceuticals Industries, Ltd.*, 2009 WL 2604919 (Fed. Cir. Aug. 26, 2009) (unpublished). In both cases, the Federal Circuit overturned the district court's grant of summary judgment of obviousness.

In *Knoll*, the patent at issue claimed a combination of hydrocodone and ibuprofen. Although prior art appeared to suggest combining these two substances, the court overturned the district court's grant of summary judgment because genuine factual disputes existed. *Id*. at 1384. For instance, the prior art did not appear to show the enhanced effects of the claimed combination. *Id*. Similarly, here, genuine issues of material facts exist with respect to all of the *Graham* factors, rendering summary judgment improper.

In *Ortho-McNeil*, the patent there claimed a combination of tramadol and acetaminophen. The prior art disclosed a four-compound combination that included these *same* compounds and two other ingredients. The Federal Circuit vacated the grant of summary

judgment because the patentee's expert testimony regarding "the understanding of one skilled in the art" as well as the expert's explanation that "drug interactions are complicated and unpredictable" raised material issues of fact. *Id*. at *3. In this case, the prior art is even further removed from the claimed invention than the prior art in *Ortho-McNeil*. Here, there is nothing in the prior art that taught the claimed composition of quinapril and a calcium antagonist. Glenmark's obviousness argument rests solely on its assertion that it would have been obvious to substitute quinapril for other compounds in the prior art combinations. But just as in *Ortho-McNeil,* plaintiffs' experts have raised genuine and material fact issues, including the level of ordinary skill in the art, the understanding of one skilled in the art, the scope and content of the prior art, and secondary considerations, thereby casting serious doubt on Glenmark's allegations. Summary judgment is therefore improper and Glenmark's motion should be denied.

CONCLUSION

Accordingly, for the foregoing reasons, plaintiffs respectfully request that this Court deny Glenmark's motion for summary judgment that claims 1-4, 7 and 10 of the '244 patent are invalid.

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Respectfully submitted

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